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<p>(21) International Application Number: PCT/US99/21612 (22) International Filing Date: 12 October 1999 (12.10.99) (30) Priority Data: 60/108,805 17 November 1998 (17.11.98) US (71) Applicant (for all designated States except US): OR-THO-MCNEIL PHARMACEUTICAL, INC. [-/US]; U.S. Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): VAN KAMMEN, Daniel, P. [US/US]; 22 Edgewood Road, Neshanic Station, NJ 08553 (US). (74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson &amp; Johnson, One Johnson and Johnson Plaza, New Brunswick, NJ 08933 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i></p>
<p>(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN TREATING POST TRAUMATIC STRESS DISORDER (57) Abstract Anticonvulsant derivatives useful in treating post traumatic stress disorder, are disclosed.</p>		

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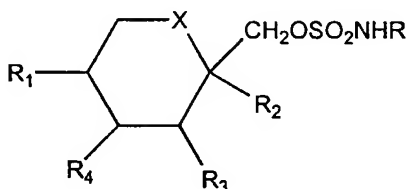
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## ANTICONVULSANT DERIVATIVES USEFUL IN TREATING POST TRAUMATIC STRESS DISORDER

### BACKGROUND OF THE INVENTION

5 Compounds of Formula I:



are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E., Nortey, S.O., Gardocki, J.F., Shank, R.P. and  
10 Dodgson, S.P. *J. Med. Chem.* 30, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught J.L. *Bioorganic & Medicinal Chemistry Letters* 3, 2653-2656, 1993). These compounds are covered by US Patent No.4,513,006. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials  
15 of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., *Epilepsia* 36 (S4) 33, 1995; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, *Epilepsia* 36 (S4) 33, 1995), and is currently  
20 marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures in approximately twenty countries including the United States, and applications for regulatory approval are presently pending in several additional countries throughout the world.

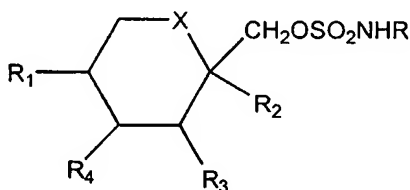
Compounds of Formula I were initially found to possess anticonvulsant activity  
25 in the traditional maximal electroshock seizure (MES) test in mice (SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., *Epilepsia* 35 450-460, 1994). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. More recently topiramate was found to effectively

block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24, 73-77, 1996).

- 5      Preclinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate will be effective in treating post traumatic stress disorder.

## DISCLOSURE OF THE INVENTION

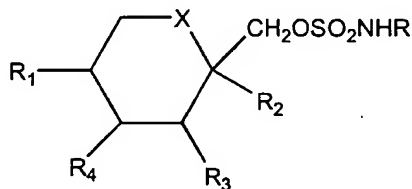
- 10      Accordingly, it has been found that compounds of the following formula I:



wherein X is O or CH<sub>2</sub>, and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined hereinafter are useful in treating alcohol addiction and abuse.

## 15      DETAILED DESCRIPTION OF THE PREFERRED EMBODIEMENTS

The sulfamates of the invention are of the following formula (I):

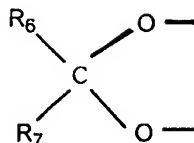


wherein

X is CH<sub>2</sub> or oxygen;

- 20      R<sub>1</sub> is hydrogen or alkyl; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen or lower alkyl and, when X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> may be alkene groups joined to form a benzene ring and, when X is oxygen, R<sub>2</sub> and R<sub>3</sub> and/or R<sub>4</sub> and R<sub>5</sub> together may be a methylenedioxy group of the following formula (II):



wherein

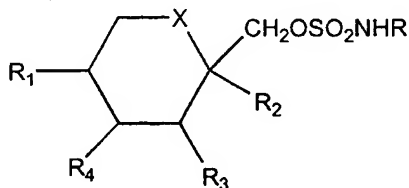
- R<sub>6</sub> and R<sub>7</sub> are the same or different and are hydrogen, lower alkyl or are alkyl and are  
 5 joined to form a cyclopentyl or cyclohexyl ring.

R<sub>1</sub> in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> may  
 10 combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R<sub>4</sub> and R<sub>5</sub> are defined by the alkatrienyl group =C-CH=CH-CH=.

A particular group of compounds of formula (I) is that wherein X is oxygen and both R<sub>2</sub> and R<sub>3</sub> and R<sub>4</sub> and R<sub>5</sub> together are methylenedioxy groups of the formula (II), wherein R<sub>6</sub> and R<sub>7</sub> are both hydrogen both alkyl or combine to form a spiro  
 15 cyclopentyl or cyclohexyl ring, in particular where R<sub>6</sub> and R<sub>7</sub> are both alkyl such as methyl. A second group of compounds is that wherein X is CH<sub>2</sub> and R<sub>4</sub> and R<sub>5</sub> are joined to form a benzene ring. A third group of compounds of formula (I) is that wherein both R<sub>2</sub> and R<sub>3</sub> are hydrogen.

The compounds of formula (I) may be synthesized by the following methods:

- 20 (a) Reaction of an alcohol of the formula RCH<sub>2</sub>OH with a chlorosulfamate of the formula ClSO<sub>2</sub>NH<sub>2</sub> or ClSO<sub>2</sub>NHR<sub>1</sub> in the presence of a base such as potassium *n*-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):



(b) Reaction of an alcohol of the formula  $RCH_2OH$  with sulurylchloride of the formula  $SO_2Cl_2$  in the presence of a base such as triethylamine or pyridine at a temperature of about  $-40^\circ$  to  $25^\circ$  C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula  $RCH_2OSO_2Cl$ .

5 The chlorosulfate of the formula  $RCH_2OSO_2Cl$  may then be reacted with an amine of the formula  $R_1NH_2$  at a temperature of about  $40^\circ$  to  $25^\circ$  C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

10 (c) Reaction of the chlorosulfate  $RCH_2OSO_2Cl$  with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula  $RCH_2OSO_2N_3$  as described by M. Hedayatullah in Tet. Lett. p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein  $R_1$  is hydrogen by catalytic hydrogenation, e.g. with a noble metal and  $H_2$  or by heating with  
15 copper metal in a solvent such as methanol.

The starting materials of the formula  $RCH_2OH$  may be obtained commercially or as known in the art. For example, starting materials of the formula  $RCH_2OH$  wherein both  $R_2$  and  $R_3$  and  $R_4$  and  $R_5$  are identical and are of the formula (II) may be obtained by the method of R. F. Brady in Carbohydrate Research, Vol. 14, p. 35 to 40  
20 (1970) or by reaction of the trimethylsilyl enol ether of a  $R_6COR_7$  ketone or aldehyde with fructose at a temperature of about  $25^\circ$  C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Volaa 38, No. 22, p. 3935 (1973).

25 Further, carboxylic acids and aldehydes of the formulae  $RCOOH$  and  $RCHO$  may be reduced to compounds of the formula  $RCH_2OH$  by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about  $0^\circ$  to  $100^\circ$  C, e.g. as described by H.O. House in "Modern  
30 Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of formula I: may also be made by the process disclosed in 5,387,700, which is incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below and above the plane of the drawing, of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> on the 6-membered ring. Preferably, the oxygens of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

Post Traumatic Stress Disorder (PTSD) is a complicated neurobehavioral disorder involving multiple neurobiological systems that mediate cognitive, emotional and behavior processes, which may be dysregulated in PTSD (Neurobiological and Clinical consequences of Stress: From normal adaptation to PTSD. Edited by M.J. Friedman, D.S. Charney and A.Y. Deutch. Lippincott Raven Publishers, Philadelphia, 1995). While most traumatic events lose their impact over time, symptoms of PTSD seem to increase over time and can be elicited by minor psychological trauma. A kindling animal paradigm has been proposed with reference to emotional memory in PTSD symptomatology. Kindling has thus been hypothesized as a possible mechanism in PTSD (Robert M. Post, Susan R.B. Weiss, Mark Smith, HE LI and Una McCann. Implications for the evolution and treatment of Post Traumatic Stress Disorder. Annals of the New York Academy of Sciences Volume 821, 1997).

Topiramate has been shown to be effective in rodent models of kindling seizures, (A. Wauquier and S. Zhov, Epilepsy Res. 24 73-77, 1996 in press).

For treating post traumatic stress disorder, a compound of formula (I) may be employed at a daily dosage in the range of about 32 to 512 mg, usually in two divided doses, for an average adult human. A unit dose would contain about 16 to 128 mg of the active ingredient.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives

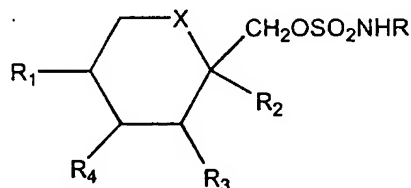
include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated  
5 or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable solutions may also be prepared in which case appropriate stabilizing agents may be employed. Topiramate is  
10 currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

15       The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository and the like from about 25 to about 200 mg of the active ingredient.



## WHAT IS CLAIMED IS:

1. A method for in treating post traumatic stress disorder, comprising  
 5 administering to a mammal afflicted with such condition a therapeutically effective amount for treating such condition of a compound of the formula I:

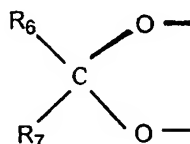


wherein

X is  $\text{CH}_2$  or oxygen;

- 10  $\text{R}_1$  is hydrogen or alkyl; and

$\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$  are independently hydrogen or lower alkyl and, when X is  $\text{CH}_2$ ,  $\text{R}_4$  and  $\text{R}_5$  may be alkene groups joined to form a benzene ring and, when X is oxygen,  $\text{R}_2$  and  $\text{R}_3$  and/or  $\text{R}_4$  and  $\text{R}_5$  together may be a methylenedioxy group of the following formula (II):



15

wherein

$\text{R}_6$  and  $\text{R}_7$  are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

- 20 2. The method of claim 1 wherein the compound of formula I is topiramate.  
 3. The method of claim 1, wherein the therapeutically effective amount is of from about 32 to 512 mg.  
 4. The method of claim 1, wherein the amount is of from about 16 to 128 mg.